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THE BURDEN OF THE NEUROCOGNITIVE IMPAIRMENT ASSOCIATED WITH *PLASMODIUM FALCIPARUM* MALARIA IN SUB-SAHARAN AFRICA

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Abstract. The burden of *Plasmodium falciparum* malaria has been estimated traditionally in terms of infections and mortality. Neurocognitive sequelae have recently been identified that add to the burden caused by this parasite. We have attempted to provide estimates of the neurocognitive burden based upon more recent estimates of the population at risk and a detailed review of published studies in sub-Saharan Africa. There is little data on which to estimate the burden, and considerable limitations in extracting the data from the published studies to provide these estimates. However, we estimate that at least 1,300–7,800 children will have neurologic sequelae following cerebral malaria in stable endemic areas per year. The figure is likely to be considerably higher, since these estimates do not include neurocognitive impairment following non-cerebral malaria in children or adults in stable endemic areas, or populations in low stable or epidemic areas.

INTRODUCTION

Throughout the last century, the burden of malaria in the world was largely estimated in terms of infection and mortality. Over the last 15 years, it has become apparent that malaria causes significant morbidity in terms of neurologic and cognitive impairment. This represents a hidden and poorly defined public health consequence of malaria, particularly in Africa. It has been difficult to assess the contribution of the neurocognitive complications to the burden of malaria due to a paucity of relevant data, differences in methodologies used to describe disability, and few attempts to articulate severity or duration of these disabilities.

Plasmodium falciparum is responsible for almost all the mortality from malaria and is the only species that appears to directly affect the central nervous system (CNS) causing neurologic deficits and cognitive sequelae[1] and epilepsy. It is the most common cause of malaria in the world, with the World Health Organization (WHO) estimating that more than 85% of *P. falciparum* malaria occurs in sub-Saharan Africa,[2] where children bear the brunt of the of the disease.

In this report, we review the spectrum of neurocognitive sequelae following *P. falciparum* malaria, with particular emphasis on children in Africa and methodologic issues related to estimating burden across Africa. We use the review of available evidence to provide a best estimate of the burden of neurocognitive sequelae following *P. falciparum* malaria in 2000, using updated figures of the populations at risk in Africa.[3]

METHODOLOGY

Literature search. To identify the spectrum and frequency of neurocognitive impairment associated with *P. falciparum* malaria, a bibliographic research was conducted using the National Library of Medicine via PubMed and Medline search engines of relevant published literature from 1960 to 2002. Key phrases used included falciparum malaria and the following terms: morbidity, cerebral, neurologic, sequelae, cognition, psychological, impairment, disability, epilepsy, and Africa. Bibliographies of reviews were browsed to identify additional articles, particularly those from WHO and United Nations sources. In addition relevant doctoral theses were reviewed. The years of the study were identified to avoid presenting data twice on the same children.

Definition of neurocognitive sequelae. For the purposes of this report, neurocognitive sequelae are defined as impairment of neurologic or cognitive function. The neurologic impairment consists of loss of function in motor, including coordination, speech, vision, and hearing domains, as well as epilepsy (Table 1). Cognitive and language impairment are defined in Table 1. Behavior difficulties are also included in the neurocognitive sequelae.

Estimating the frequency of neurocognitive sequelae. *Population at risk.* The populations at risk of various intensities of *P. falciparum* infection have been recently updated by the Burden of Malaria in Africa project to inform the Disease Control Priorities Program. In 2000, it was estimated that there were 557 million people living in areas of sub-Saharan Africa climatically suitable for malaria transmission (Table 2).[3] Among this population, approximately 188.6 million children less than 15 years of age were exposed to stable endemic malaria transmission conditions and consequently at risk of severe complications following infection.

To calculate the children at risk of developing cerebral malaria (CM), we used estimates of annualized CM that were abstracted from surveillance data between 1991 and 1996.[3] This reflected a total of 219,441 person-years exposure to risk among children resident within the hospital's catchment area between 0 and 9 years old and with an incidence of CM cases presenting to hospital from the combined sites of 1.12/1,000/year. Although the rates of CM varied considerably between settings with the highest rates in areas of low-to-moderate malaria transmission and the lowest rates in areas of intense malaria transmission, the malaria conditions prevailing across the sites included in this analysis broadly represent the spectrum of transmission across much of stable, endemic malaria in sub-Saharan Africa, and thus a single point estimate has been used to describe these risks.

The case fatalities of CM, even under optimal management conditions, are high. We assumed that clinical conditions that progress to severe cerebral involvement would not survive in the absence of intensive clinical management, and as such CM cases surviving hospital admission probably reflect most of

TABLE 1
Description of neurocognitive sequelae

	Description
Ataxia	Unsteadiness in gait or fine manipulation
Hemiparesis/ monoparesis	Weakness of one side of the body (hemiparesis) or limb (monoparesis). Rarely complete paralysis (hemiplegia)
Severe motor deficit	Quadriparesis (weakness of all four limbs) with spasticity. Unable to walk. Often associated with severe learning difficulties, epilepsy, and blindness.
Dysphasia/dysarthria	Difficulty in talking; the studies do not distinguish between language impairment and difficulty in talking
Behavioral difficulties	Parents report difficulty in controlling behavior of the child. Child is aggressive and does not obey commands.
Severe learning difficulties	Severe cognitive impairment as assessed by a clinician, manifesting as difficulty in understanding commands.
Visual impairment	Cortical blindness i.e., unable to navigate through doors or pick up objects, but eyes are normal
Hearing impairment	Does not appear to hear, does not turn towards sound
Cognitive impairment	Scoring at least 2 standard deviations below the age-specific unexposed group mean or below the 2.0 centile of the unexposed group results for normally distributed and skewed data, respectively. Some tests have established *a priori* defined criteria for impairment
Language impairment	As in cognitive impairment
Epilepsy	Two or more seizures following discharge, unprovoked by fever

the surviving CM cases in a community, and thus exposed to the risk of sequelae. Those who do not reach a hospital would contribute to the mortality component of the malaria burden. From a review of available published studies of hospitalized CM cases since 1990, the estimated median case-fatality rate was 17.0% (interquartile range [IQR] = 13.0, 21.7%).[3] As such, one can assume an annual incidence of surviving CM among children 0–9 years old within easy reach of a hospital setting of between 0.874/1,000/year and 0.975/1,000/year. The populations exposed to residual sequelae are likely to be those located within reach of a hospital. An estimate of the proportion of the population living within 15 km of hospital care was 36%, a figure used in previous disease burden calculations and derived from national demographic and health surveys.[4]

The differences in the denominators used to calculate risk (0–9 years old) and the application to continental populations at risk (0–15 years old) under stable endemic risk were corrected to allow for the residual numbers of cases in older age groups (10–14 years old). Assuming a risk of exposure to a sequel between 0.874 and 0.975/1,000, year and a total at-risk population 0–15 years old living within 15 km of a hospital of 67,900,379 (188,612,165 × 0.36), then the total numbers of at-risk CM survivors is likely to be between 59,344 and 66,203 each year.

RESULTS

We considered studies reporting neurocognitive impairment in any infections with *P. falciparum* ranging from asymptomatic parasitemia to consequences of severe disease.

Infection with *P. falciparum*. We were able to identify only two studies that have examined the effect of asymptomatic parasitemia on cognition, but they were conducted outside Africa. A study in Yemen demonstrated that parasitemic children performed worse than non-parasitemic children in fine motor tasks, but not in cognitive tests.[5] In a randomized control trial of chemoprophylaxis in Sri Lankan school children, chloroquine prophylaxis improved the scholastic performance during a malaria transmission season.[6] Whether these results are applicable to African children in different endemicity settings is unknown. Another study examining the long-term effects of malaria chemoprophylaxis during early childhood in The Gambia upon learning abilities later in life is currently being analyzed (Jukes M, unpublished data).

Clinical disease. We were not able to identify any studies that measured the effect of acute febrile episodes caused by *P. falciparum* on cognition. It is estimated that there were approximately 213.6 million clinical episodes of malaria in Africa in 2000. The duration of uncomplicated acute infections depends upon the immunity, but the median duration of illness is 5.1 days (IQR = 4.3–6.0).[3] Thus, through the sheer number, these infections may contribute to the neurocognitive burden of malaria.

Sequelae of severe *P. falciparum* malaria. Most studies of persistent sequelae have been studied in the context of the severe clinical syndromes that require admission to a hospital. In African children, the commonest complications precipitating admission to a hospital are severe anemia, respiratory distress, recurrent convulsions, and impaired consciousness, including CM.[7] Hypoglycemia is a common metabolic dysfunction occurring in 8.4% of the children admitted with malaria to a Kenyan district hospital,[8] and may have a strong impact on neurocognitive outcome.

A variety of sequelae have been described following severe *P. falciparum* malaria in children (Table 1). The pathogenesis of sequelae has been recently reviewed.[1] Most reports of sequelae described the neurologic deficits detected on discharge from a hospital following CM, but the frequencies of these sequelae have varied considerably from one study to another. Thus, in an overview conducted in 1997, it was estimated that 10.9% of the children with CM had neurologic deficits following discharge from a hospital.[9]

While most of the neurologic deficits are usually seen at the

TABLE 2
Sub-Saharan Africa estimates for population at risk in 2000[3]

	Birth	0–4 years	5–14 years	>14 years	Total
At risk in southern Africa	435	2,049	3,709	8,687	14,445
Low stable/epidemic risk	5,280	22,018	34,668	69,126	125,812
Stable endemic risk	17,330	73,351*	115,261*	228,105	416,717
Total	23,045	97,418	153,638	305,918	556,974

* Numbers for which the risk was calculated.

time of discharge, others appear later in life for some survivors. The deficits seen on discharge may disappear within a short period of time or persist with the effect of either mortality or permanent impairment. Measuring the burden contributed at each point in time is difficult due to the absence of follow-up studies, which can be used to measure incidence. Estimation of the true burden therefore becomes difficult.

We were able to identify 27 published studies that examined children on discharge from a hospital for neurologic sequelae following severe *P. falciparum* malaria in Africa (Table 3). Although there may be inherent biologic reasons for variations in the descriptions provided from different centers across the diverse malaria ecologies in Africa, a more important consideration is the inconsistency in patient recruitment, observational methods, and duration of follow-ups.

Frequency of neurocognitive sequelae. To estimate the frequency of the major neurologic deficits following CM, we identified four studies from Africa that used the WHO criteria for CM[7] and assessed all children on discharge from the hospital Table 4). Most of these studies were performed in research units in Malawi, Kenya, and The Gambia attached to referral hospitals. Two additional studies assessed children after discharge with a follow-up period of more than 18 months, the time when one would expect most of the recovery of function to occur. No data were available on the residual sequelae among populations in southern Africa or areas of low endemicity in Africa, and no information is available on adult populations.

We assessed a recent study performed in Kenya in children based upon rigorous epidemiologic data that identified all cases of CM admitted to a district hospital over an eight-year period who were between six and nine years old in 2000 and 2001 (Table 5). This study suggested that neurocognitive impairment is much more extensive. For example, there was an increased prevalence of epilepsy after CM (odds ratio [OR] = 4.4, 95% confidence interval [CI] = 1.4–13.7) and malaria plus complicated seizures (M/S) (OR = 6.1, 95% CI = 2.0–18.3) compared with the unexposed children. Twenty-four percent of the CM and M/S groups had at least one impairment (as defined by less than two standard deviations of the mean or 2% of the control group) in any of the domains assessed.[10]

Thus, the numbers of children with a persistent impairment in at least one domain from The Gambian and Kenyan studies each year following CM brain insult would be between 1,306 (59,344 × 0.02) and 7,812 (66,203 × 0.118) (Table 5). Further studies are needed to determine if the frequency of sequelae detected in these studies occur in other areas. For example, the estimate for epilepsy is likely to be considerably higher if one takes into consideration epilepsy following non-cerebral malaria.

Limitations of the studies. In the review of the studies, a number of limitations were identified. They can be categorized as follows.

Differences in definition. There are considerable differences in the definition of the parameters used in these studies. Thus, some studies use the strict definition of CM proposed by the WHO,[7] while others use a more functional definition, e.g., child with seizures.[11,12] These differences are further confounded by differences in the pathogenesis of the strictly defined clinical complications. Thus, impaired consciousness, the clinical hallmark of CM, can be caused by seizures, postictal state, systemic disturbances, or a primary neurologic condition.[9] Clinicians often use different terms to describe similar neurologic deficits (Table 3). Some impairments were not assessed by standardized tests, e.g., audiometry for hearing. The definition of cognitive impairment varied considerably from clinical judgment to standardized psychological tests. Some studies did not identify the proportion of children with impairment, but compared the scores between cases and controls.[13] Furthermore, the definition of cognitive impairment varied, although most psychological tests use at least two standard deviations below the mean of the control or normal population.

Selection bias. Many investigators appear to have been selective about the cases that are included in the study, without giving either the criteria of selection or the denominator of cases admitted during the period of recruitment. Furthermore, some studies were randomized control trials of interventions that may have affected the outcome.[14–16] This makes the generalization of the results difficult to compare with other areas in Africa.

Differences in assessment. Clinicians and assessors vary in their ability to assess children. The ability of clinicians to detect neurologic deficits varies according to experience and the circumstances in which the examination is conducted. Most studies do not report the interobserver variation or experience of the clinicians in assessment techniques. In the studies shown in Table 3, mild sequelae were often detected when the child was examined in an outpatient setting.[15] There are considerable differences in the tools of assessment. This is particularly applicable to the neuropsychological tests, in which none of the studies have used the same tests, although many of them have the same theoretical basis, e.g., Kaufman Assessment Battery for Children modified for studies in Kenya[17] and Senegal.[13] Some of these differences have come about by the necessary adaptation of the tests to local circumstances.

Confounding factors. Most studies have followed-up children after discharge from a hospital. It is rarely possible to take into consideration the pre-morbidity condition of the child, despite the effect that this may have on the assessment. Perinatal insults and neurodevelopment prior to the illness is particularly important.[18] Birth weight and nutritional status may be important in the context of malaria.[19] Concurrent factors, such as iron deficiency or occult infection with human immunodeficiency virus may effect a child's assessment, particularly cognition. Some of the sequelae depend heavily on parental reporting, e.g., behavioral disturbances and seizures, and thus may be influenced by cultural perceptions of these conditions.[20]

Changes with time. Most neurologic deficits, similar to other acute insults to the brain, improve over time, with most change occurring within the first 1–2 years. Children with severe neurologic deficits often die after discharge from a hospital. Thus, in a study of Kenyan children who were followed up after admission with CM, mortality was increased compared with those in the community (Mung'ala-Odera V and others, unpublished data). Other sequelae, however, may only become evident as the child grows older, e.g., deficits in language may only be detected when the child begins to use complicated language.[21] Epilepsy caused by malaria can only appear at a later date, with the cumulative incidence increasing with time, as occurs after other CNS infections.[22]

A number of post-malaria syndromes have been described,

TABLE 3
Studies examining neurologic sequelae following severe malaria

Country of study	Period of study	Criteria of cases	Total no. of cases studied (% mortality)	No with sequelae (% of survivors)	Sequelae described
Senegal[11]	1960–1961	Convulsions	88 (25)	16 (24)	Not reported
Uganda[33]	1966	Coma	20 (30)	1 (7)	Monoparesis
Senegal[34]	1967	Coma and convulsions	34 (9)	7 (23)	Ataxia, blindness, deafness, hemiplegia, motor, behavior
Senegal[35]	Not indicated	Altered consciousness or convulsions	235 (32)	12 (8)	Not reported
Malawi[36]	1975	Coma	39 (28)	1 (4)	Spastic cerebral palsy
Zaire[37]	1976–1977	Convulsions, motor deficits and/or impaired consciousness	131 (?)	8 (?)	Hemiplegia, cortical blindness
Ghana[38]	1979	Alteration of the sensorium and/or convulsions	43 (5)	3 (7)	Hemiparesis, psychosis, auditory and visual hallucinations
Tanzania[39]	1979–1981	Impairment of consciousness, acute convulsions and focal cerebral signs	66 (18)	10 (20)	Hemiparesis, epileptic fits, hemihyperthesia, organic psycho syndrome
Malawi[40]	1987–1988	Blantyre coma score ≤4	131 (15)	12 (11)	Hemiparesis, hypotonia, limbs spasticity, cerebellar ataxia, exrapyramidal tremor
The Gambia[12]	1988	Coma and convulsions	377 (16)	29 (9)	Decerebration, hemiplegia, ataxia, aphasia, blindness, spasticity, psychosis, epilepsy
Nigeria[41]	1986–1988	Coma, seizures, irritability, and signs of meningeal irritation	75 (20)	10 (17)	Hemiparesis, psychosis, aphasia, amnesia
Ghana[42]	1989	Unarousable coma	113 (5)	16 (15)	Increase tone, could not walk, could not sit, could not talk, blindness, deafness, hyperactivity, convulsions
Kenya[43]	1989–1990	Unarousable coma, unable to localize pain	42 (19)	5 (15)	Seizures, ataxia, hyperreflexia, inability to sit/walk
Zambia[44]	1990–1991	Blantyre coma score ≤4 not fixing and following	83 (19)	2 (3)	Paresis
Kenya[45]	1994–1996	Unarousable coma	160 (16)	29 (22)	Visual and hearing deficits, hemiparesis, hypertonia, mental retardation, monoparesis, quadra paresis, speech impairment, inability to sit/stand
Nigeria[46]	1987–1989	Unarousable coma but with purposeful response to stimuli or worse	61 (18)	8 (16)	Cranial nerve palsies, speech deficits, intellectual impairment, monoparesis, cortical blindness
Nigeria[47]	1987–1988	Unarousable coma, Adelaide coma score ≤6	78 (21)	11 (18)	Hemiplegia, seizures, monoparesis, quadriplegia, memory impairment, hearing loss, dysarthria, dysphasia, blindness
Congo[48]	1988–1989	Coma lasting for at least 2 hours	170 (15)	13 (9)	Seizures, cortical blindness, hemiparesis, hypotonia, muscle tone, disorders, ataxia, speech disorders, hemichorea
Nigeria[49]	1990–1991	Unarousable coma but with purposeful response to stimuli or worse	54 (17)	5 (11)	Motor weakness, cortical blindness, loss of neurologic milestones
The Gambia[50]	1990	Blantyre coma score ≤2	41 (29)	5 (9)	Hemiplegia, generalized weakness and irritability
Burundi[51]	1992–1993	Unarousable coma, Blantyre coma score ≤3	56 (9)	4 (8)	Not described
The Gambia[15]	1992–1994	Blantyre coma score ≤2	624 (22)	114 (23)	Paresis, ataxia, hearing defects, visual defects, aphasia/dysarthria, behavior problems, developmental regression, seizures
Kenya[52]	1994	Unarousable coma, unable to localize pain	65 (11)	8 (14)	Hemiplegia, spastic quadriplegia, cognitive and speech problems, epilepsy
Nigeria[53]	1991	Coma	45 (13)	11 (28)	Hearing loss, cortical blindness, dyskinesia, echolalia, aphasia, hemiplegia
Togo[54]	1994–1995	Coma, severe alteration of consciousness	230 (22)	15 (8)	Aphasia, hemiplegia, speech impairment, oculomotor paralysis, ataxia
Kenya[16]	1995–1998	Blantyre coma score ≤3	340 (13)	24 (17)	Visual impairment, quadriplegia, developmental delay, hemiplegia, epilepsy, ataxia, speech impairment
Nigeria[55]	1992–1994	Unarousable coma (but with purposeful response to stimuli or worse) with or without convulsions	103 (22)	12 (15)	Cortical deafness, abnormal gait, aphasia, hypotonia, motor deficits

TABLE 4
Frequency of neurocognitive impairment on discharge following cerebral malaria*

Study	Malawi (1987–1988)[40]		The Gambia (1988)[12]		Nigeria (1991)[53]		Kenya (1992–1994)[45]		Nigeria (1992–1994)[47]		Sequelae present on discharge
	Discharge	>6 months	Discharge	>6 months	Discharge	>6 months	Discharge	>6 months	Discharge	>6 months	%
Number studied	131		308		45		160		78		
No. assessed	111		265	23	39	10	134		62	62	
No. with deficits	12		32	11	11	2	29		11	7	
Duration of follow-up (months)	1			6		1–6	1 week		0	12	
Ataxia	2		6	0	4	0	0		0	0	0.38
Hemiparesis	4		23	6	1	0	2		4	4	1.64
Severe motor deficit	2		9	2	1	0	4		0	0	0.66
Dysarthria/aphasia	NR		9	2	3	1	0		1	0	0.82
Behavior difficulties	NR		NR	NR	1	0	1		0	0	0.76
Severe learning difficulties	NR		NR	NR	0	1	4		0	0	0.95
Visual impairment	NR		11	2	2	0	5		3	0	0.47
Hearing impairment	NR		NR	NR	3	0	6		1	1	0.68
Convulsions	NR		NR	3	0	0	0		1	1	

* NR = not recorded.

of which post-malaria neurologic syndrome (manifesting as psychosis and seizures)[23] and post-malaria cerebellar syndrome (ataxia)[24] are the best documented. These syndromes last only a couple of months and are rarely reported in Africa.[25] Thus, they may not contribute significantly to the neurocognitive burden. It is unclear if either acute infections or the post-malarial syndromes have any long-lasting effects on cognitive function, or cause epilepsy.

DISCUSSION

In Africa, there is little accurate data to estimate the burden of neurocognitive impairment caused by *P. falciparum* malaria. Based upon the data extracted and presented in this report, at least 1,000 children are likely to be left with serious neurologic impairment following CM across areas of stable endemic malaria in Africa each year. This is the minimum estimate and is lower than that produced by Murphy and Breman[26] using a different methodology. This estimate does not include sequelae following non-cerebral malaria or sequelae in an additional 368 million people exposed to some risk of malaria infection or disease, including those located in southern Africa, low endemic or epidemic areas, or adults. Furthermore, these estimates of sequelae are likely to underestimate the burden simply by virtue of the limited periods of follow-up in studies to-date, particularly for epilepsy, which may become more evident with time, and difficulties with school caused by language and cognitive impairment. The current estimates are crude and should be interpreted with caution due to the inherent weaknesses of the available data and absence of relevant data for estimation purposes.

These present, albeit, crude estimates signal the importance of *P. falciparum* malaria in causing disability in sub-Saharan Africa. *Plasmodium falciparum* may be one of the most important causes of acquired disability in malaria-endemic areas of the continent, leading to long-term personal impairments that may impede economic development in countries plagued by malaria. Many of the sequelae described in this review are life-long impairments in quality of life and provide a chronic economic and palliative care burden to households. The economic costs of the disability within households may be overt or through the loss of potential earnings. The cost of drugs or supportive care, if available, depends entirely upon the types of disability. For the management of epilepsy, the minimum simplest regimens may amount to 20–30 US dollars per year per patient.[27] Many children with severe motor impairments are unlikely to attend school, particularly when household resources for education are scarce. Furthermore, their contri-

TABLE 5
Persistent neurocognitive impairments following cerebral malaria in Africa* (minimum estimates)

	The Gambia (1992–1994)[47]		Kenya (2000–2001)[25]†	Number with impairments
Time after admission to assessment	6	18	64 (IQR 40–78)	–
Number assessed	452	13	152	–
Deficit				
Ataxia	5 (1.1)	3 (0.7)	6 (3.9)	415–2,185
Motor deficits	7 (1.6)	4 (0.9)	5 (3.3)	534–2,582
Hearing impairment	3 (0.7)	1 (0.2)	0	0–132
Visual impairment	2 (0.4)	1 (0.2)	0	0–132
Speech difficulties	4 (0.9)	4 (0.9)	14 (9.2)	534–6,091
Behavior difficulties	4 (0.9)	1 (0.2)	1 (0.7)	119–463
Severe learning difficulties	4 (0.9)	2 (0.4)	0	0–265
Epilepsy	1 (0.2)	1 (0.2)	10 (6.6)	119–4,369
Impairment in one domain	20 (4.4)	10 (2.2)	18 (11.8)	1,306–7,812

* Values in parentheses are percentages. IQR = interquartile range.
† Removes the background prevalence in the control group.

bution to the household income is limited. Finally, children surviving CM are more likely to die than those not exposed to CM, particularly if they have neurologic deficits (Mung'ala-Odera V, unpublished data) or epilepsy.[20,28–30]

Assessment of disability is difficult, but forms an integral part of the WHO estimation of disease burden, which is summarized as the disability adjusted life years (DALYs).[31,32] This is a quantitative measure of years of life lost due to premature mortality plus years of life disabled. Disability for any given condition is calculated as a weight, which is equivalent to some fraction of a death. These weights are based upon western estimates and are unlikely to be applicable to malaria-endemic areas. Given the paucity of data in malarious areas, it is difficult to provide even a crude estimate of the disability component of DALYs for malaria.

It is clear from this review that more comparable, standardized, longer follow-up data are needed to provide accurate estimates of the burden of *P. falciparum* malaria on neurocognitive impairment. More data on the sequelae following CM is required, particularly from areas of different endemicity, and among older children and adults and different ethnic groups. Much of the assessment of cognition was assessed with western psychological tests that had been adapted for local circumstances. It is unclear if this adoption is adequate,[19] and psychological tests that can assess similar parameters need to be developed in the context of different cultures. Studies with longer follow-up after exposure to CM are required, in particular to detect epilepsy. The extent of neurocognitive impairment, either transient or permanent, following less severe *P. falciparum* malaria needs to be documented. Only with these studies can an accurate estimate of the burden of *P. falciparum* malaria in sub-Saharan Africa be determined.

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